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- Regularly weigh risks versus benefits of the components of a complex pharmacotherapy regimen for patients with bipolar disorder

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A Systematic Review of Complex Polypharmacy in Bipolar Disorder: Prevalence, Clinical Features, Adherence, and Preliminary Recommendations for Practitioners

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and Joseph F. Goldberg, MD^{b,*}

ABSTRACT

Objective: Extensive combination pharmacotherapy regimens for bipolar disorder have gained increasing use in routine practice in ways that outpace data from evidence-based clinical trials. The present review examined the prevalence of complex pharmacotherapy regimens in bipolar disorder patients and sought to characterize factors that most influence polypharmacy prescribing patterns.

Data Sources: The authors independently systematically searched the MEDLINE, PsycINFO, and Embase databases for English-language observational/naturalistic or randomized controlled polypharmacy trials, using the keywords *bipolar* and *polypharmacy* or *bipolar* and *combination treatment* and *pharmacotherapy*.

Study Selection: From among 3,566 publications, 49 ultimately met study inclusion criteria.

Data Extraction: Information was obtained regarding prevalence rates of extensive polypharmacy as well as clinical characteristics and naturalistic outcomes for patients with simple (≤ 2) or complex (≥ 3) regimens of psychotropic agents.

Results: A weighted mean percentage of 32.7% of bipolar outpatients (4,535/13,863) taking ≥ 3 psychotropic medications was identified. Factors associated with complex polypharmacy use include female sex, White race, age > 50 years, history of psychosis, greater burden of depressive illness, subtherapeutic dosing, lower treatment adherence, more extensive psychiatric comorbidity, and a greater history of suicide attempts.

Conclusions: Extensive or complex combination pharmacotherapy regimens are common in many patients with bipolar disorder and often reflect greater overall illness severity. Naturalistic studies do not point to better outcomes for patients receiving more complex drug regimens, suggesting likely confounding by indication, high severity, or comorbid conditions. Formal clinical trials are needed to identify optimal drug combinations and durations when using ≥ 3 psychotropic medications to treat patients with bipolar disorder.

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Clinical Points

- Although extensive combination pharmacotherapy is common in many patients with bipolar disorder, naturalistic studies do not point to better outcomes for patients receiving more complex drug regimens.
- Simplifying regimens, optimizing doses prior to adding another agent, deprescribing ineffective medication, and carefully considering risks and benefit versus lack of benefit of each medication may improve clinical care while incorporating known factors that place the patient at risk.

Once shunned as a sign of suboptimal care, the use of complex pharmacotherapy has increasingly become the norm in the treatment of bipolar disorder.¹⁻⁷ In part, elaborate medication combinations may reflect the potential shortcomings and incomplete efficacy of traditional monotherapies such as lithium, as well as the complexity of a disorder in which comorbidities are common.^{8,9} Domains of psychopathology in bipolar disorder span such diverse dimensions as mood, behavior, psychosis, cognition, speech-language, personality, and circadian dysrhythmias—making it unlikely that any single drug could reasonably provide comprehensive efficacy. The expansion of newer US Food and Drug Administration (FDA)-approved pharmacotherapy options across all phases of bipolar disorder during the past two decades also bears consideration as contributing to polypharmacy. Clinicians may sometimes implement new agents as augmentations without necessarily discarding existing medications, in the hopes of either additive or synergistic effects, or perhaps fear of clinical deterioration if existing medications were deprescribed. The absence of clear guidelines for when to discontinue certain medications—such as antidepressants or antipsychotics—after an acute episode may further add to overall pharmacotherapy burden. “Carryover” of medications prescribed by previous treaters may also sometimes become folded into current drug regimens without deliberation as to their necessity, relevance, tolerability, or ongoing efficacy.

To date, there has been little formal review in the literature regarding the nature and extent of complex combination pharmacotherapy, the theoretical if not empirical rationale for specific combinations, its use in subpopulations, and impact on clinical outcome. The aims of the current review were therefore as follows:

1. To differentiate simple from complex pharmacotherapy and review prevalence of the latter across studies in bipolar disorder patients;
2. To identify clinical characteristics associated with the use of complex pharmacotherapy in clinical practice; and
3. To provide preliminary recommendations to clinicians about when complex pharmacotherapy for bipolar disorder is most often rationale-based and likely to be clinically advantageous.

METHODS

The systematic review was prepared in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; <http://www.prisma-statement.org>) following a registered publicly available protocol.

Preliminary Screening

A general, preliminary search was carried out on MEDLINE. The initial search terms used were *bipolar disorder* and *polypharmacy*. Results were screened to determine specific inclusion and exclusion criteria. The initial search yielded 175 results from 1981 to 2019. Following review of abstracts, full articles, and references, the following criteria were imposed: for inclusion, studies needed to (1) specify a diagnosis of bipolar disorder; (2) focus on polypharmacy of psychotropic medications; (3) include multiple, diverse individuals (ie, single case reports or small case series were excluded); (4) be related at the clinical (rather than preclinical) level; and (5) be English-language publications. Exclusion criteria involved studies that (1) did not include or specify a bipolar disorder diagnosis (and if included bipolar disorder, was a not separate section from other diagnoses); (2) did not focus on adjunctive treatments other than pharmacologic (eg, psychosocial, chronobiological); (3) failed to identify the number of medications taken by study subjects; (4) focused primarily on medication side effects rather than the demographics of medication prescribing; (5) were case reports, book formats, basic science reports, review articles, practice guidelines, opinion articles, or consensus statements without empirical data presentations; (6) reported on patients under 18 years old; and (7) were non-English language publications.

A subsequent MEDLINE search using the terms *bipolar disorder* and *combination treatment* and *pharmacotherapy* through the year 2020 yielded 3,566 results.

Information Sources and Search Criteria

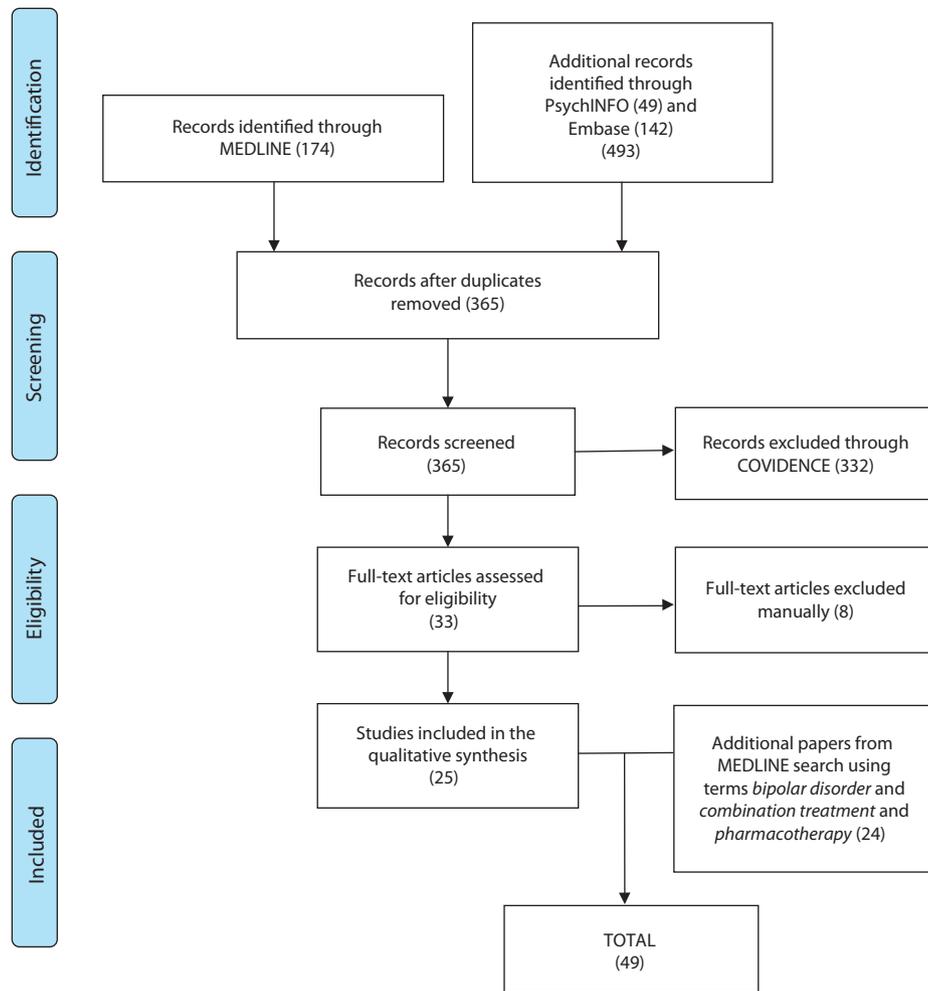
From this preliminary search, we determined a protocol to be used for a systematic literature review on polypharmacy in bipolar disorder with a focus on demographics and prescribing patterns. We limited our search to records published in peer-reviewed journals and without publication date restrictions. Sources of information were accessed through MEDLINE, PsycINFO, and Embase and uploaded into COVIDENCE (www.covidence.org), a technology platform to assist with systematic reviews through data extraction, collection, and sorting format that in 2015 was adopted as the standard platform for Cochrane Reviews. Search criteria for MEDLINE, PsycINFO, and Embase included bipolar disorder, polypharmacy, limited to English language, and limited to adulthood (age 18 years and older). Duplicate records were automatically removed by COVIDENCE.

Study Selection

Our intent was to focus mainly on studies that report on prevalence rates and/or outcomes of bipolar patients

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Figure 1. PRISMA Flowchart of Included and Excluded Studies



receiving complex polypharmacy defined as ≥ 3 psychotropic medications. We therefore did not include studies of an adjunctive drug versus placebo added to treatment as usual (TAU) if TAU did not explicitly entail at least 2 drugs, or studies for which the total number of psychotropic drugs taken was not specified.

Following the aggregation of records from these 3 search engines, all of the authors independently examined and sorted manuscripts. Reviewers were blinded from each other. If there was not information in the abstract, full texts were accessed and reviewed according to inclusion and exclusion criteria.

Data Collection and Processing

Individual results were reviewed by the authors to resolve disagreements and reach a final consensus based on strict inclusion and exclusion criteria. The consensus constituted articles for final, full reading and review (see Results and Discussion section). Risk of biases in individual studies and across studies have been addressed in the limitations paragraph in the Discussion section.

RESULTS

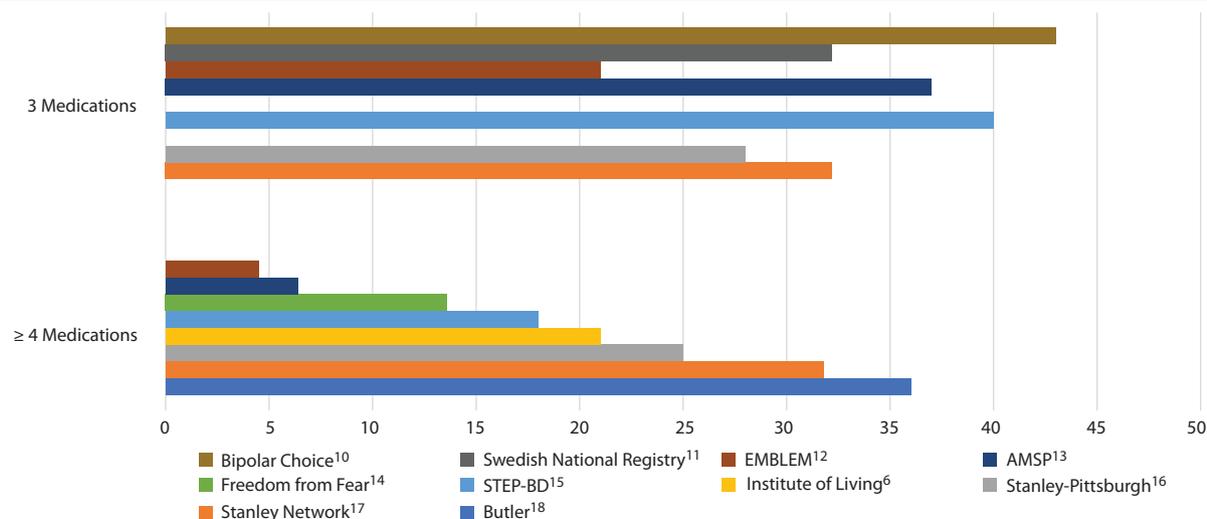
Further Study Selection

The 174 results from the initial MEDLINE search using the terms *bipolar disorder* and *polypharmacy* were uploaded into COVIDENCE. The following searches through PsycINFO yielded 49 additional results and through Embase, 142 additional results. These 3 search engines yielded a total of 493 results. Removal of duplicates resulted in 365 records, which were fully screened, blinded, following inclusion and exclusion criteria. Following resolution of disagreements by the authors, through the COVIDENCE platform, 33 records were selected for full review. These articles were then manually sorted, and 3 removed due to only abstract and poster being accessible, 2 were supplements, 1 was found to be Spanish-language only, and 2 included schizophrenia and bipolar disorder together. From this manual review and final reading, 25 articles from 1997 to 2019 were selected for initial qualitative analysis.

Hand-screening of publications generated from a second MEDLINE search, which yielded 3,566 results, resulted in 24

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Figure 2. Representative Percentages of Bipolar Patients Taking 3 or ≥ 4 Psychotropic Medications During Post-Acute Maintenance Treatment Across Major Studies



Abbreviations: AMSP = Institut für Arzneimittelsicherheit in der Psychiatrie, EMBLEM = European Mania in Bipolar Longitudinal Evaluation of Medication, STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

separate reports that met study criteria, increasing the final number of relevant publications to a total of 49.^{1–6,10–52} A PRISMA flowchart for study selection is presented in Figure 1.

Main Clinical Features

Definitions of polypharmacy and complex polypharmacy. *Polypharmacy* itself can be defined both conceptually and concretely. For the purposes of research, a more concrete, operative form is preferred as “the use of two or more psychiatric medications in the same patient.”^{2–5,7} We shall refer to the use of only 2 medications as *simple polypharmacy*. *Complex polypharmacy* has generally been defined in the literature as the use of either ≥ 3 medications (eg, Nierenberg et al¹⁰) or ≥ 4 medications (eg, Golden et al,⁶ Goldberg et al,¹⁵ Kim et al²⁰). For the present study we define *complex polypharmacy* as “the use of 3 or more psychotropic medications.”

Prevalence of complex polypharmacy and trends over time. Figure 2 presents a summary of reported prevalence rates of bipolar patients taking either 3 or ≥ 4 medications based on studies from the literature search reporting those distinctions. From the studies identified in the figure, we calculated a weighted pooled mean percentage of 27.8% (2,614/9,414) taking (only) 3 medications and 22.3% (2,660/11,935) taking ≥ 4 medications. Discounting overlapping cases, a combined pooled total of 32.7% (4,535/13,863) took ≥ 3 medications.

In addition to the studies listed in Figure 2, several others met our definition of complex polypharmacy but reported prevalence rates of ≥ 3 medications without distinguishing more specific breakdowns. These included (a) a 2006 German cross-sectional study (published in 2010)²¹ in which antidepressants were the most often coprescribed drug among the 6.6% of patients who received ≥ 3 medications, (b) a study of 93 German private practitioners³⁶ in which 5% of bipolar patients were prescribed ≥ 3 medications in both 2009

and 2018 (quetiapine was the most commonly coprescribed drug in 2018), (c) a 4-month survey of 16 Asian countries encompassing 348 patients (Research on Asian Psychotropic Prescription Pattern for Bipolar Disorder [REAP-BD])²⁰ in which 34.3% took ≥ 3 medications, (d) a cohort of 80 bipolar outpatients from the Charité-University Medicine (Berlin)³ in which nearly all took a mean of 3.8 medications over 3 months, and (e) a cross-sectional study of 169 Brazilian bipolar outpatients³⁷ in which 19% took ≥ 3 medications.

Trends over time suggest a rising frequency of combination pharmacotherapy over the past two decades. For example, observations from the National Institute of Mental Health (NIMH) intramural program¹ indicated a sharp increase in polypharmacy regimens over a 22-year period among combined groups of refractory bipolar and unipolar mood disorder patients, with use of ≥ 3 medications increasing from 3.3% in the mid-to-late 1970s to 9.3% in the early 1980s to 34.9% in the mid-to-late 1980s to 43.8% in the early 1990s, irrespective of patient age. A Danish registry study³⁸ found significant increases from 2000 to 2011 in rates of prescribing lithium plus an anticonvulsant or plus an antipsychotic, a doubling in the rate of coprescribing an antidepressant plus anticonvulsant or plus antipsychotic, and a 4-fold rise in the prescribing of an anticonvulsant plus antipsychotic. The European Institut für Arzneimittelsicherheit in der Psychiatrie (AMSP) Project found that the number of prescribed drugs (lithium, anticonvulsant, antipsychotic, or antidepressant) rose steadily from a mean of 2.1 during 1994–1997 to 2.9 during 2006–2009.¹³ By contrast, data from the Scottish registry²² found remarkably stable rates of complex polypharmacy from 2009 to 2016 (noted in Table 1).

In a number of studies, complex polypharmacy was more commonly encountered in bipolar disorder than in other disorders, although geographic variations were evident. For example, a retrospective study of German outpatients⁴ (n = 300) reported monotherapy as most common in

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Table 1. Summary Findings on Outcomes During Complex Polypharmacy in Observational Studies of Patients With BD

Authors	Study Type (n)	Main Findings
I. Bipolar Disorder		
Frye et al ¹	Retrospective review of outcomes among National Institute of Mental Health (NIMH) intramural study participants (n = 178)	Increasing numbers of medications needed to achieve remission over successive years from 1974 to 1996
Adeponle et al ²	Cross-sectional review of 2 regional Nigerian outpatient clinics (n = 278)	92% took ≥ 2 medications; any polypharmacy in 21.1% of affective disorder patients versus 46.1% with schizophrenia
Adli et al ³	3-month survey of German outpatient academic centers; ChronoRecord software captured a mean of 114.7 days per patient (n = 80)	93.4% received at least simple polypharmacy (mean = 3.8 medications). Most (72.5%) had bipolar I disorder (BD I); mean of 2.43 hospitalizations; 28.8% deemed disabled
Assion et al ⁴	Retrospective study of 10 German clinics (n = 300)	75% took ≥ 2 medications. Antipsychotics were used in 87%–97% of individuals with bipolar disorder or schizoaffective disorder
Baek et al ⁵	BD I or II patients across 10 Korean academic hospitals since 2009 (n = 1,447)	In all phases, polypharmacy picked for initial treatment in > 80% (most favored was mood stabilizer and antipsychotic). Antipsychotics prescribed in > 80% across all phases. Antidepressants were used in 15%–40%
Golden et al ⁶	Longitudinal cohort study of discharges of inpatients with bipolar disorder from the Institute of Living (n = 2,712)	Complex polypharmacy more common in BP I depression (48.2%) than BP I manic (12.3%) and BP II patients and associated with being female and White and having psychotic features, comorbid borderline personality disorder, posttraumatic stress disorder, or another anxiety disorder. Lithium use not associated with complex polypharmacy
Nierenberg et al ¹⁰	Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness) trial comparing adjunctive quetiapine or lithium to existing medications in adjunctive lithium recipients (n = 240)	Comparable (nonsignificantly different) rates of improvement with either augmentation; lithium better tolerated than quetiapine
Wingård et al ¹¹	Naturalistic 1-year follow-up after index mania using the Swedish National Registry (during 2006–2014); 5,713 hospitalizations for mania (3,772 subjects)	Among 204 subjects taking ≥ 3 medications (lithium plus divalproex plus an atypical antipsychotic), risk for medication switch, discontinuation, or rehospitalization was lower than for those taking antipsychotic monotherapies. An earlier analysis ¹⁹ showed that rehospitalization rates 1 year after an index manic episode were comparable among complex pharmacotherapy recipients and those taking fewer medications
Gonzalez-Pinto et al ¹²	2-year naturalistic follow-up after index mania; Bipolar EMBLEM (European Mania in Bipolar Longitudinal Evaluation of Medication) cohort (n = 1,076)	Combination therapy groups (both simple and complex) had significantly lower rates of treatment adherence, more frequent anticholinergic use, and more tremor and sexual dysfunction than seen with olanzapine monotherapy. Monotherapy versus combination-therapy groups did not differ in time to discontinuation, improvement, or recovery
Peselow et al ¹⁴	2-year naturalistic follow-up after index manic episode in New York Freedom from Fear Program; treatment with lithium ± divalproex ± carbamazepine (n = 1,312)	Significantly higher relapse rates at 2 years for those taking ≥ 3 medications (41.9%) or 2 mood stabilizers (43.9%) than those taking 1 mood stabilizer (22.8%)
Goldberg et al ¹⁵	Patterns of lithium, anticonvulsants, antidepressants, and antipsychotics examined from bipolar disorder subjects entering STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) in 1999–2005 (n = 4,035)	Risk of complex polypharmacy increased if subjects had ever taken an atypical antipsychotic, had ≥ 6 lifetime depressive episodes, attempted suicide, and had an annual income of \$75,000 or more
Levine et al ¹⁶	Review of 1995–1996 outpatient bipolar disorder registry (n = 457)	No differences observed in monotherapy or simple or complex polypharmacy regimens across age, sex, education, marital status; clinical outcomes not reported
Post et al ¹⁷	Naturalistic treatment outcomes in the Stanley Bipolar Network (n = 429)	A mean of 2.98 medications was needed over 18 months to achieve remission for at least 6 months; responders took fewer antidepressants or antipsychotics than nonresponders
Weinstock et al ¹⁸	Retrospective chart review from Brown University/Butler Hospital (n = 230)	Complex polypharmacy (≥ 4 drugs) occurred in 36% of cases. Complex polypharmacy recipients were more likely to be female and depressed, have a comorbid anxiety disorder, and have a history of a suicide attempt. No difference was found based on ethnicity or race, civil status, insurance, or history of prior hospitalizations
Kim et al ²⁰	Research from the Asian Psychotic Prescription Pattern for Bipolar Disorder (REAP-BD) study from 16 Asian countries (n = 348)	Simple or complex polypharmacy associated with younger age, more extensive inpatient treatment, shorter duration of untreated illness, less use of antidepressants, more use of anxiolytics, mania polarity at illness onset, and overweight/obesity
Quante et al ²¹	2006 German outpatient 3-month epidemiologic study (n = 306)	Combination therapy was more common in patients with mixed episodes (58%) or rapid cycling (55%) than pure-polarity phases of illness
Lyll et al ²²	Prescribing data from electronic Scottish Morbidity Records from 2009 to 2016 (n = 23,135)	Complex polypharmacy rates changed minimally from 2009 (15%) to 2016 (17%)

(continued)

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Table 1 (continued).

Authors	Study Type (n)	Main Findings
Baldessari et al ²³	2005 prospective study of adherence from US national data sample from 131 randomly selected prescribing psychiatrists (n = 429)	Nonadherence was rarer than with monotherapy and was associated with alcohol dependence, youth, greater affective morbidity, side effects, comorbid obsessive-compulsive disorder (OCD), and recent recovery from mania or hypomania. Unrelated factors: sex, diagnostic subtypes, other comorbidities
Baldessarini et al ²⁴	US national health claims from 2000 to 2004 examining polypharmacy and adherence (n = 7,406)	Initial prescriptions involved only 1 medication in 67% of patients and 2 or more in 33% of patients. At 1 year, 31% of patients received monotherapy and 32% received any polytherapy. Polypharmacy was less likely with lithium than with anticonvulsants. Anticonvulsant adherence at 1 year was greatest with lamotrigine
Bauer et al ²⁵	Self-reported daily medication analysis over 6 months (n = 450)	75% took stable simple or complex polypharmacy. About half of stable polypharmacy patients took an antidepressant. No pattern found between stable drug combinations
Bauer et al ²⁶	Self-reported mood and medication adherence over 6 months (n = 312)	No significant association between adherence and daily number of medications versus pills. Subjects with lower adherence took smaller doses of mood stabilizers
Bjørklund et al ²⁷	Cohort study from annual cross-sectional examination of medication use (1995–2012) in the Danish Psychiatric Central Research Register (n = 20,618)	Simple or complex polypharmacy increased significantly from 1997 (55.7%) to 2012 (61.0%) except in patients over age 70 years. The proportion receiving lithium, typical antipsychotics, and benzodiazepines/sedatives decreased. The proportion receiving antidepressants, atypical antipsychotics, and anticonvulsants increased. The proportion of patients on treatment with antidepressants decreased from 20.5% in 1997 to 12.1% in 2012, and monotherapy decreased from 47.7% to 23.9%
Garver et al ²⁸	Retrospective claims database (1998–2004) comparing racial differences in polypharmacy (n = 1,113)	More Black individuals received ≥ 2 medications from different classes (41.1% compared to 34.7%) and switching or concomitant medications than non-Black individuals
Jaracz et al ²⁹	Chart review of discharges from 5 psychiatric facilities in Poland (n = 127)	Considering only mood stabilizers, second-generation antipsychotics, and lamotrigine, 61% of patients took 2, 21.3% took 3, and 1 took 4 medications. Mood stabilizer + atypical antipsychotic was the most common simple polypharmacy (48%). No association between polypharmacy and age, duration of illness, and global improvement
Peh and Tay ³⁰	Record review of two private outpatient practices in Singapore from 1999 to 2003 (n = 121)	46% received combinations of mood stabilizers, antipsychotics, and antidepressants. 34% incurred a delayed correct diagnosis by > 2 years
Sachs et al ³¹	Cross-sectional assessment of personality features and polypharmacy in consecutive patients from Massachusetts General Hospital bipolar clinic (n = 89)	Low openness, low extraversion, and low conscientiousness may be associated with increased psychotropic medication use
Kupfer et al ³²	Cohort study within the Stanley Center Bipolar Disorder Registry (Pittsburgh) (1995–1999) (n = 2,839)	More than a third took complex polypharmacy; half had attempted suicide
Fung et al ³³	Secondary analysis of adult bipolar disorder participants in the Bipolar CHOICE trial (n = 482)	Complex polypharmacy found in 43% and associated with nonadherence but not greater side effect burden. 16% of complex polypharmacy recipients achieved remission. Remission was less likely in those with poor adherence, comorbid social or generalized anxiety disorder, or BD I vs II diagnoses
Adachi et al ³⁴	Cross-sectional nationwide survey of 176 Japanese outpatient clinics (MUSUBI) (n = 3,130)	Patients took a mean of 3.5 ± 0.8 medications. Number of drugs was associated with poor social adjustment, psychiatric comorbidities, and duration of illness
II. Bipolar Depression		
Greil et al ¹³	Observational cross-sectional prescription data from European psychiatric hospitals in inpatients from 1994 to 2009 (n = 2,231)	81.3% received antidepressants (7.8% as monotherapy), 57.9% antipsychotics, 50.1% anticonvulsants, 47.5% tranquilizers, and 34.6% lithium. Use over time decreased with lithium and increased for anticonvulsants, antipsychotics, and tranquilizers; was stable for antidepressants; and increased for quetiapine, lamotrigine, and valproate
Howland ³⁵	Cross-sectional assessment of depressed inpatients with bipolar disorder at Pittsburgh Western Psychiatric Institute and Clinic (n = 69)	Polypharmacy more common among patients with psychosis; antidepressant use observed in about half of depressed bipolar patients

schizophrenia patients (44.4%), followed by 16.1% in those with bipolar disorder and 11.9% in those with schizoaffective disorder. By contrast, in a cross-sectional Nigerian study (n = 278),² simple or complex polypharmacy rates were lower in bipolar disorder (21.1%) than in schizophrenia (46.1%). In general, at least simple polypharmacy is often the initial treatment strategy in greater than 80% of bipolar disorder patients,⁵ usually as a combination of mood stabilizer and antipsychotic. A Taiwanese study⁴⁰ points out that 71% of prescriptions in bipolar disorder involved

between-class polypharmacy while 17% involved within-class polypharmacy.

Both simple and complex polypharmacy in special populations—notably, bipolar disorder in pregnancy and old age—have received limited study. One study of 533 pregnant women with bipolar disorder in Australia⁴¹ found that 30% were prescribed simple polypharmacy. A study of a Danish registry enrolling 336 pregnant women with bipolar disorder in 1997–2002⁴² found that slightly less than 6% took a combination of an antidepressant plus an anticonvulsant

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mood stabilizer plus at least 1 other psychotropic medication, about 4% took an antidepressant plus an atypical antipsychotic plus at least 1 other psychotropic medication, 4% took an antidepressant plus anticonvulsant plus atypical antipsychotic, 4% took an antidepressant plus lithium plus at least 1 other psychotropic medication, about 2.5% took an antidepressant plus lithium plus an atypical antipsychotic, slightly more than 2% took an antidepressant plus lithium plus an anticonvulsant mood stabilizer, and less than 2% took lithium plus an anticonvulsant plus an atypical antipsychotic.

Among older adults with bipolar disorder, a Dutch cross-sectional study (n = 101) of mainly outpatients⁴³ identified any polypharmacy in 31.7% of subjects; a median took 2 psychotropic compounds (most often involving a pairing of lithium, sedatives, antidepressants, antipsychotics, or anticonvulsant mood stabilizers), and nearly one-third took >6 medications in total (including both psychotropic and nonpsychotropic medications). A cross-sectional study of 1,443 elderly Canadian bipolar disorder outpatients⁴⁴ found at least simple polypharmacy in 81.5%. In the European AMSP database,⁴⁵ triple drug therapy was significantly rarer in acutely manic patients older versus younger than age 70.

Clinical features associated with complex polypharmacy.

Table 1 summarizes main findings from 31 of the 49 studies drawn from the final literature search that reported outcome data for bipolar disorder patients taking complex polypharmacy regimens.

Varied clinical features have been associated with complex polypharmacy. A German retrospective chart review of 80 bipolar disorder outpatients³ found a median age of 38 years old, 50% male and 50% female, 72.5% with bipolar I disorder (BD I) and 27.5% bipolar II disorder (BD II), 50% single and 50% married, and a history of 2.43 hospitalizations, with 28.8% on disability. A 2002 study characterizing a cohort of 2,839 outpatients³² identified through the Stanley Center Bipolar Disorder Registry found a median age of 40.1 years, 65.4% women, and 90% White, with 60% having completed some college, 30% having completed college, and 64% currently unemployed. Importantly 50.3% had attempted suicide, and the disparity between education level and employment was noted. A 2008 Singaporean retrospective chart review of 121 bipolar disorder outpatients notes that 58% were employed, 48% married, with 7% a diagnosis of BD I, 76% BD II, and 7% bipolar disorder not otherwise specified (BD NOS).³⁰ No psychotic symptoms were observed in 75% of the population; 65% had never been hospitalized, 9% had past suicide attempts, and 16% had had electroconvulsive therapy (ECT).³⁰ This study took particular care to comment on the diagnostic complexity of bipolar disorder, elaborating on the delay in diagnosis as contributing to polypharmacy as well as the challenges in achieving full remission.

In the 2009 report based on Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) data,¹⁵ likelihood of either simple or complex polypharmacy was found to be higher if individuals were ever on treatment with an antipsychotic, if there was a history of ≥ 6 lifetime episodes of depression, history of suicide attempts, or annual

income of greater than \$75,000. A history of psychosis, age at onset, BD I versus II, rapid cycling, prior hospitalizations, and alcohol and substance use were not found to alter risk of polypharmacy, although rapid cycling was still ascertained a predictor for extensive depression, antidepressant use, and suicidal behavior.¹⁵ Another STEP-BD report focusing on the naturalistic use of ≥ 2 antipsychotics in bipolar subjects⁴⁶ (evident in 10% of the study group) found an increased overall burden of adverse effects and greater service utilization but no differences in global functioning or symptom status as compared to those taking ≤ 1 antipsychotic.

A 2014 chart review of 231 inpatients with BD I diagnoses³¹ found that any form of polypharmacy was more likely in depressed females with comorbid anxiety disorders and a history of suicide attempts, and no difference was found based on ethnicity or race, civil status, insurance, or history of prior hospitalizations. However, the data from this study were based on a population of 94% White and 91% non-Hispanic individuals,¹¹ and contrastingly a study focusing on racial differences in prescribing in bipolar disorder found that Black individuals tended to have more Medicaid and Medicare complementary services as well as Axis I diagnoses than non-Black individuals.²⁸ Additionally, more Black individuals received ≥ 2 medications from different classes (41.1% compared to 34.7%), and switching or use of concomitant medications was higher in Black individuals.²⁸

Aside from race, other variables studied in relation to polypharmacy in bipolar disorder have included personality characteristics. Sachs et al³¹ examined personality styles and found low openness, low extraversion, and low conscientiousness to be associated with increased psychotropic medication use. A 2017 prospective cohort study of 2,712 inpatients⁶ concluded that variables associated with complex polypharmacy included White race, female sex, psychotic features, and comorbid diagnosis of borderline personality disorder, posttraumatic stress disorder (PTSD), or anxiety disorders. Interestingly, substance use was not associated with polypharmacy.⁶

Table 2 summarizes demographic and clinical features associated with complex polypharmacy based on the present literature review.

Medication types within polypharmacy. Trends in medication types within simple or complex polypharmacy regimens were generally consistent throughout the studies. A 2016 nationwide register-based cohort study from 1995 to 2012²⁷ found that the proportion of lithium, benzodiazepines, and typical antipsychotics decreased over time, while the number of antidepressants, anticonvulsants, and atypical antipsychotics has increased.

In the AMSP Project,³⁹ among patients taking at least 3 medications, the most commonly observed combinations (each 1%–2%) were a selective serotonin reuptake inhibitor (SSRI) plus lithium and quetiapine, an SSRI plus lithium and lamotrigine, an SSRI plus mirtazapine with lithium or divalproex or venlafaxine, or lithium plus mirtazapine plus venlafaxine; incident rates of 1.1% each were observed with an SSRI plus olanzapine plus lithium, lithium plus

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Table 2. Clinical Characteristics Associated With Complex Polypharmacy in Bipolar Disorder Patients

Characteristic	Observations
Sex	Female ^{6,23}
Race	White ⁶
Age	Above 50 years in some studies, ¹⁹ ; no relation between age and medication number in others ^{1,16,29}
Psychosis	Present more often than absent ^{6,35}
Bipolar disorder subtype	Remission less likely in complex pharmacotherapy subjects with bipolar I than with bipolar II disorder diagnoses ¹³
Medication dosage	Generally lower than in monotherapy ⁴⁰
Depressive illness burden	High ¹⁵
Treatment adherence	Lower than with fewer medications ³³
Association with adverse effects	No clear additive burden ³³
Comorbid personality disorders	Borderline personality disorder ⁶
Other comorbid psychiatric conditions	Posttraumatic stress disorder ⁶ ; remission less likely in complex pharmacotherapy subjects with social or generalized anxiety disorder ³³ or other anxiety disorders ¹⁸
History of suicide attempts	Typically ≥ 1 ^{15,18}
Personality traits	Low levels of extraversion, conscientiousness, and openness ^{5,31}

Table 3. Provisional Recommendations for the Use of Complex Polypharmacy in Bipolar Disorder Pending Development of a Systematic, Empirical Database to Guide Decision-Making

Recognize the relative antimanic (eg, lithium, divalproex) versus antidepressant (eg, lamotrigine) properties of mood-stabilizing agents as component drugs within a complex polypharmacy regimen

Simplify regimens by using multipurpose agents as appropriate (eg, quetiapine, lurasidone, cariprazine targeting both depression and anxiety; adjunctive gabapentin targeting anxiety, insomnia, and neuropathic pain)

Favor optimized doses of existing agents before adding other within-class compounds (eg, multiple antipsychotics)

Strive to change only one pharmacology variable at a time whenever feasible to minimize confusion about composite outcomes

Minimize abrupt stopping and starting of medications before the effects of an adequate trial can reasonably be judged

Regularly weigh risks versus benefits of existing components of a complex pharmacotherapy regimen

Deprescribe medications that are deemed ineffective (after an adequate trial has elapsed) or inappropriate (eg, antidepressants or psychostimulants during manic or mixed episodes)

Periodically reassess the relevance of each component of a pharmacotherapy regimen

quetiapine plus venlafaxine, or lithium plus quetiapine plus lamotrigine. Clinical correlates or statistical predictors of complex polypharmacy in that cohort were not reported. In another contemporary multinational observational study,²⁵ 75% of those who were taking polypharmacy remained on a stable regimen for $\geq 50\%$ of days. Individual polypharmacy patterns in that study varied, with no particular combination appearing especially prominent.

Antidepressant use and complex polypharmacy. Although expert consensus guidelines generally eschew antidepressant monotherapy in bipolar disorder,⁵³ formal studies reporting on complex polypharmacy involving antidepressant use were surprisingly scarce. As noted in Table 1, the European AMSP study¹³ found decreased use of lithium; increased use of antipsychotics, anticonvulsants, and tranquilizers; and no change regarding antidepressant use from 2009 to 2018. A total of 81.3% of that study group received antidepressants (7.8% as monotherapy), and 57.9% took antipsychotics. Least associated with polypharmacy were lithium, divalproex, and carbamazepine, while most associated included antidepressants and atypical antipsychotics. In

a Danish registry study,²⁷ antidepressant monotherapy declined by about half from 1997 to 2012. Another 1997 study of 69 bipolar depressed inpatients found that 90% received one “anti-manic” drug, most often lithium, and 50% were maintained on antidepressants.³⁵ In the Asian REAP-BD study,²⁰ the combination of mood stabilizer and antipsychotic was most commonly used as the initial treatment strategy during maintenance phase therapy (80%), with antidepressant use ranging from 15% to 40%.⁵

Adherence and complex pharmacotherapy in bipolar disorder. A number of studies addressed polypharmacy in relation to medication adherence. As noted in Table 1, a health claims review by Baldessarini et al²⁴ found that when examining adherence with anticonvulsants, patients were more likely to be adherent with lamotrigine as compared to valproate, carbamazepine, oxcarbazepine, and lithium, while nonadherent patients were more often prescribed divalproex, carbamazepine, and oxcarbazepine. Adherent patients also were less likely to use drugs or alcohol, more likely to have a comorbid anxiety disorder, and more likely to be treated by a psychiatrist rather than a primary care physician. Although adherent patients utilized 55% more ambulatory visits and 44% more emergency services compared to nonadherent individuals, overall, there was a 27% decrease in hospitalizations for all reasons. A prospective study by this team²³ found that nonadherence during polypharmacy was associated with comorbid alcohol dependence, youth, greater affective morbidity, side effects, comorbid obsessive-compulsive disorder (OCD), and recent recovery from mania or hypomania. Factors unrelated to polypharmacy nonadherence included sex, diagnostic subtypes, and other comorbidities. The authors concluded that OCD and hypomania could reflect ambivalence and denial of symptoms related to bipolar disorder and that some of the consequences of the disease on the patient could go unrecognized, thus leading to more complex and aggressive regimens with “vicious” cycles of diminishing adherence. Others have suggested, rather, that a complex medication regimen itself could contribute to nonadherence; however, this has been contradicted by suggestions that concurrent psychotropic medications are not associated with nonadherence. Bauer et al²⁶ found no association between medication adherence and the number

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of prescribed medications or actual number of pills consumed per day.

Outcomes. Functional and symptomatic outcomes for patients receiving extensive polypharmacy are difficult to judge from naturalistic studies because of the very high likelihood of confounding by indication and protopathic bias—that is, a higher number of medications is likely the result, rather than the cause, of greater illness severity and a presumably poorer previous response to simpler treatment regimens. This is certainly the impression generated by most observational studies linking lower remission rates with the use of more extensive medication regimens for bipolar disorder (eg, Chae et al⁴⁸), although it contrasts with findings from the Swedish registry study¹¹ showing higher rates of treatment failure (eg, relapse, rehospitalization) among monotherapy than polypharmacy recipients.

When searching the literature for controlled pharmacotherapy trials involving use of ≥ 3 psychotropic medications for any phase of bipolar disorder, we identified only a handful of studies. One randomized trial reported across 2 articles^{49,50} involved the use of 3 mood stabilizers (lithium plus divalproex plus lamotrigine) versus 2 (lithium plus divalproex plus placebo) in rapid-cycling outpatients for whom lithium plus divalproex failed to achieve stabilization. That trial failed to demonstrate an advantage for triple versus double mood stabilizer therapy, although high study dropout, poor tolerability and statistical underpowering were collectively perceived to contribute to an uninformative end result with regard to undemonstrated efficacy. Another trial in 45 acute manic patients from Iran⁵² found a significantly greater reduction in mania symptoms when the 5-HT₂ antagonist ritanserin rather than placebo was added to the combination of lithium plus haloperidol. An additional small (n = 32) randomized study focusing on comorbid OCD in bipolar disorder patients⁵¹ found an advantage for reducing obsessive-compulsive symptoms with the combination of lithium plus olanzapine plus clonazepam plus topiramate versus lithium plus olanzapine plus clonazepam without topiramate.

DISCUSSION

Definitions of *polypharmacy* and *complex polypharmacy* were generally consistent throughout the literature. Polypharmacy, whether simple or complex, appears to have become the norm during acute and maintenance phases of bipolar disorder, occurring at least to some degree in more than half of adult patients. Populations with complex polypharmacy were of particular interest and concern, occurring in 21% to 43% of study populations, with bipolar depression at highest risk. Combination therapy was found to be implemented more often in women, White individuals, and those older than age 50 years. A later age may reflect lifelong attempts at varied management strategies for symptoms. Interestingly, female sex is often comorbid with anxiety disorders (social, general), PTSD, and borderline personality disorder, which were found to be clinical diagnoses associated

with complex polypharmacy in our systematic literature review. Increased combination pharmacotherapy was noted in patients with a history of psychosis, greater burden of depressive illness, and a history of suicide attempt. Greater overall illness severity is reflected in extensive or complex pharmacotherapy in bipolar disorder.

Aside from patient characteristics, clinician prescribing practices provide insight as well. Prescriptions of lithium and typical antipsychotics have decreased over time, perhaps due to need for monitoring and unwanted side effect profile. Contrastingly, prescriptions of antidepressants have remained the same or elevated, and increases have been noted in the number of patients taking antipsychotics or other mood stabilizers. Manifold explanations for this trend exist and may include prescriber reluctance to remove medications that are perceived to be possibly beneficial, the wish to try new medications and/or combinations in the hopes of improved efficacy, lack of clear standardized guidelines (resulting in subtherapeutic dosing or multiple agents), consideration of patient personality traits and subjective report, and overall rapport. Perhaps prescribing practices respond to patient characteristics of low extraversion, conscientiousness, and openness.

The observational nature of the vast majority of the literature on complex polypharmacy precludes causal relationships and invites speculation about confounding by indication (that is, a presumption that more severely ill patients “require” more medications when simpler regimens prove ineffective). Hence, it is possible that complex polypharmacy might sometimes arise from the fact that available treatments are frequently not always efficacious as monotherapy, underscoring the need for development of novel therapeutics. Only in rare instances among naturalistic studies did we observe better outcomes with polypharmacy than with monotherapy (eg, Wingård et al¹¹). Another perspective, articulated based on findings from the Stanley Bipolar Network, suggests that the phenomenology of modern-day bipolar disorder may be more inherently complex than in previous eras, such that greater numbers of medications are now needed to achieve stabilization, as suggested by Frye et al¹ and Post et al.¹⁷

At the same time, given that clinical practice may often favor complex polypharmacy as an assumed necessity for more severely ill patients, it must also be noted that other factors that drive complex polypharmacy may be poorly accounted for in naturalistic studies—such as clinicians’ failure to deprescribe ineffective medications, use of inappropriate medications (eg, antidepressants during mania or episodes involving mixed features, use of drugs with duplicative mechanisms, or the intended thymoleptic use of anticonvulsants that lack mood-stabilizing properties), or failure to optimize dosing of appropriate medications, among other considerations.

Perhaps the most fundamental unanswerable question from the present review involves insight into when complex polypharmacy could yield better clinical outcomes than simpler regimens. The veritable absence of large randomized

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trials to address this issue seems to pose one of the greatest unmet needs in modern psychopharmacology, and the practical limitations of undertaking such efforts makes it unlikely that empirical findings to guide this question are forthcoming. It remains uncertain whether inclusion of certain specific agents within a broader regimen—such as lithium or olanzapine – may either lessen the need for complex polypharmacy or improve its likelihood of success; thus, Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness) subjects taking lithium had a somewhat lesser “burden” of antipsychotic cotherapy, but not better overall outcomes,¹⁰ while in the Swedish registry study¹⁹ complex polypharmacy recipients whose regimen included olanzapine had lower rehospitalization rates.

Because complex polypharmacy more often tends to be a marker for greater illness complexity and severity, it is likely also a proxy for treatment resistance to simpler regimens. On the other hand, such inferences are difficult to draw without knowing details about the adequacy, appropriateness, and adherence surrounding possible simpler pharmacotherapy efforts that may predate complex polypharmacy for some patients. Sachs et al³¹ coined the term *ineffective complex chronic care* (ICCC) to describe patients who “remain ill despite receiving 5 or more medications for 6 or more months.”^{31(p1065)} Given our observation that one-third or more of bipolar patients receive complex polypharmacy, clinicians who encounter ICCC-type situations must differentiate pharmacologic futility despite strategic or heroic efforts to overcome true lack of efficacy from simpler regimens versus artifacts of past treatments that may have been inadequate, inappropriate, or undermined by nonadherence.

Because of the limited insight provided by the literature on complex polypharmacy, alongside the reality that many bipolar disorder patients receive extensive drug therapy regimens despite the lack of an empirical evidence base, we sought to identify basic concepts and principles that may aid clinicians in their efforts to determine the rationale and logical basis for considering complex polypharmacy. These provisional recommendations, pending the future emergence of a more rigorous clinical trials database, are summarized in Table 3.

A further recommendation relevant to the reporting of future clinical trials involving complex polypharmacy pertains to studies that randomize subjects to a particular adjunctive drug versus placebo when added to TAU. Surprisingly few existing published trials using that design

specify precisely or systematically what drugs comprise TAU, in either number or intensity of therapy, limiting the extent to which inferences can be made about the relative impact of a unique agent added to an existing complex regimen without knowledge of the appropriateness or adequacy of baseline TAU.

Limitations of the study include the use of single covariate statistical analyses to examine individual predictors rather than risk profiles; recall and confounding bias within each study; varied diagnostic bias across studies, such as the overlap between schizoaffective disorder and bipolar disorder; inpatient versus outpatient settings; differences in sample sizes and selection bias (homogenous vs non-homogenous); and regional and cultural differences in addition to pharmacoeconomic issues that have an influence on treatment decision. Importantly, psychosocial factors such as quality of patient-clinician communication and family/environmental support are factors that could not be accounted for. Children were not included in attempts to simplify the analysis. Additionally, we were unable to assess health care-related factors that might influence polypharmacy, such as prescriber discipline (eg, MD versus non-MD midlevel provider) and expertise, treatment setting (clinic versus community mental health or private practice), and extent and use of nonpharmacologic interventions (eg, individual psychotherapy, groups, day treatment programs).

Strengths of the present study include the systematic and rigorous review of articles from multiple search engines, a holistic and integrated understanding of multiple factors contributing to polypharmacy, inclusion of recent articles, and applicability to identify populations at risk for polypharmacy as well as patterns in prescribers.

Both simple and complex polypharmacy are highly prevalent and, when not strategically devised, can become unduly costly, complex, and a driver of poor adherence and excessive adverse drug effects. Naturalistic studies do not suggest better outcomes for patients receiving more complex drug regimens. Formal clinical trials are needed to identify optimal drug combinations and durations when using ≥ 3 psychotropic medications to treat patients with bipolar disorder. Strategies such as simplifying regimens, optimizing doses prior to adding another agent, deprescribing ineffective medication, and carefully considering risks and benefit versus lack of benefit of each medication can be employed for improved clinical care, all the while incorporating known factors that place the patient at risk.

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1. All of the following factors have been associated with the use of complex polypharmacy in studies of patients with bipolar disorder *except* _____.
 - a. Longer duration of illness
 - b. Higher medication doses than typically seen in simpler drug regimens
 - c. Psychosis
 - d. Low medication treatment adherence
2. Which one of the following descriptions of trends over time regarding polypharmacy for bipolar disorder is *accurate*?
 - a. An increase from about 3% to over 40% over 2 decades intramurally at the National Institute of Mental Health
 - b. A 6-fold increase in the rate of antidepressant plus anticonvulsant or antipsychotic prescribing in the Danish population from 2000–2011
 - c. Stable rates of polypharmacy in the European Institut für Arzneimittelsicherheit in der Psychiatrie Project from 1994–2009
 - d. A steady rise from a mean of 2 to 4 prescribed drugs from 2009 to 2016 in Scottish registry data
3. Amber Lynn, a 35-year-old woman with acute bipolar II depression, has been taking sertraline 150 mg/d for 1 year, duloxetine 60 mg/d for 6 months, aripiprazole 10 mg/d for 4 months, lithium carbonate 900 mg/d for 2 years, and quetiapine 50 mg/d for 1 year. Each of the following modifications to her medication regimen would be reasonable *except* _____.
 - a. Eliminate aripiprazole for lack of an FDA indication in bipolar II disorder and redundancy with another antipsychotic (quetiapine)
 - b. Optimize quetiapine dosing per its package insert instructions for bipolar depression
 - c. Discontinue lithium because it is associated with poorer adherence in polypharmacy regimens
 - d. Eliminate antidepressants sertraline and duloxetine for lack of efficacy given their lack of demonstrated efficacy after adequate trials as well as mechanistic redundancies

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